IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s): Bakulesh Khamar et al. Examiner: J.E. Graser
U.S. Patent Application Serial No.: 10/502,417 Group Art Unit: 1645
Filing Date: February 15, 2007
Entitled: THE METHOD OF TREATING CANCER

RULE 132 DECLARATION OF BAKULESH KHAMAR

Dr. Bakulesh Khamar, (M.S.), a citizen and resident of India, states and declares that:

1. I am Executive Director- Research with Cadila Pharmaceuticals, Ltd., located at Ahmedabad India ("Cadila"). Cadila has a 243,000 square feet production plant and research facility at Dholka , Ahmedabad apart from facilities at Jammu and Ethiopia. Apart from India, we have sales and distribution set-up in the United States., Africa, Russia (CIS) and Japan having world-wide employment of over 4,000 employees. Our products are registered in more than 5 continents and 90 countries, and are being promoted by strong network of distribution channels and professionals. It is one of the largest privately held pharmaceutical companies in India and has been in active operation for over 59 years. We have both, proprietary and generic products on sale or in development covering diversified therapeutic segments and specialties. My own experience in management and research at Cadila spans 15 (Fifteen) years. I am fully familiar with research and drug development, in the U.S. and distribution and monitoring of usage of new small molecule drugs and biologics. I am a co-inventor, co-applicant of the above identified U.S. patent application and am fully familiar with its prosecution history including the office actions and references cited and responses.

2. Cadila was the first Indian company to gain approval by the U.S. FDA for clinical trials in India and since then has filed further four such applications. Our research and quality control staff has over 390 professionals.

3. I address points of the lack-of-enablement rejection, applied to the claims now pending in the application, and in the supporting specification and drawings and have a clear opinion based on my experience, education, and analysis of the present case that the claims are enabled, as I further explain below.

4. The actual composition used in the specification examples demonstrating medical effect (as in Examples 4 to 9), was the one provided in Example 1a which consists of 0.5×10^9 heat killed whole cells of *Mycobacterium w* in 0.1 ml. But the other disclosed compositions are also usable.

5. The dose administered was:
   - 0.1 ml as per example 4 to 8
   - 0.2 ml initial dose as per example 8b, paragraph [0108]
   - 0.3 ml as per Example 9

6. The route of administration in all examples of administration was intradermal, through intramuscular is also disclosed separately.

7. The frequency of administration was:

- Once a month
  Example 5 of paragraph [0093], line 4,
  Example 6 of paragraph [0097], line 4

- Once every two weeks
  Example 8(a) of paragraph [0105], line 7
  Example – 8(b) of paragraph [0108], line 6-8

- Once a week
  Example 8(a) of paragraph [0105], line 6
  Example 4, Case 1, para [0085], line 9 and case 3, para [0089], line 11.

- Biweekly
  Example 9 of paragraph [0113], line 6

8. Regarding support for enablement as to muscle invasive bladder cancer, I draw attention to the following facts:

(a) Muscle invasive bladder cancer – Para [0099] of the application states that

'Thus *Mycobacterium w* is effective in achieving complete remission and maintaining it'.

Complete remission is also called complete response and it means the disappearance of all signs of cancer in response to treatment. This is the on professional understanding of complete remission.

Source: National Cancer Institute's Dictionary of Cancer Terms. Available: "Complete Remission." (Access date August 9, 2010, Link:

http://www.cancer.gov/Templates/db_alpha.aspx?CdrID=45651) A copy is filed herewith.

Thus, the present invention provided complete response to therapy and not just to reduced bladder lesions as indicated by the Examiner (Page No. 7, line 30, of the Office Action).

9. The Examiner has also raised a question as to the effect of the *Mycobacterium w* composition in view of radio therapy. I draw attention to the following facts:

i. 'Local control rates with radiation alone for muscle invading tumors have been disappointingly low and radiation as mono therapy has largely been abandoned. (See Kaufman et al Annal of Oncology 2006, 17 (Supplement 5) v.106-v112. A copy is filed herewith.

ii. Various modalities have been tried at least since 1985 to improve outcomes of bladder pressuring approach for muscle invasive bladder cancer.

The approaches include trans urethral bladder resection (TURBT) with radiotherapy and /or chemotherapy. See William et al, Cancer Suppl, April 15, 2003 Vol. 97, No. 8, 2115-2119. A copy is filed herewith.

iii. Example 6 illustrates complete remission of muscle invasive bladder cancer using *Mycobacterium w* and radiotherapy in absence of TURBT in all cases (100% complete response). All remained disease free till the end of follow-up.

None of the subjects noticed any side effect of radiotherapy and/or *Mycobacterium w*. Thus Example 6 illustrates effect of *Mycobacterium w* in achieving complete remission and maintaining it. It also illustrates lack of side effects of *Mycobacterium w* as well as radiotherapy.

10. Currently, there is no systemic therapy for treatment of superficial bladder cancer. Currently superficial bladder cancer is treated by TURBT followed by intravesical BCG and / or chemotherapy.

Example 5 illustrates efficacy of *Mycobacterium w* in absence of TURBT and intravesical therapy.

11. Regarding efficacy of Mycobacterium w in refractory cancer as a stand alone therapy, I note that treatment by the present invention of cancer refractory to standard therapy, as in the specification cases 1 and case 3, illustrates efficacy of *Mycobacterium w* in refractory cancer as a stand alone therapy.

12. The present specification teaches fully on how to enable making of and using the present invention. As to making, the production of the *Mycobacterium w* is fully described and it is, per se, a well known biological species. Pharmaceutical composition including it are well described and is being commercialized by Cadila under brand name Immuvac. As for using, the specification relies on well known per se methods of dose selection and administration protocols and adapting those to particular circumstances can be done without undue experimentation.

13. Cadila is conducting following clinical trials under supervision of U.S. and India health authorities.

a) Study NCT 00694798 (USFDA): "Study of *Mycobacterium w* in BCG Refractory Superficial Transitional Cell Carcinoma of Bladder (STCC)."

The protocol admits patients who have failed to achieve disease-free state at six months after initiation of therapy or patients who have recurrence of tumor within three months after completion of treatment or adequate retreatment, but excluding patients with certain co-morbidity conditions, including i.e., immuno-compromised.

The investigations are at several prominent hospitals in India. The investigators have no difficulty, to the best of my information and belief, in using the present invention. The health regulatory authorities who approved the trials had no difficulty, to the best of my information and belief, in understanding how to use the invention.
b) Study NCT00525408 (US FDA) : "A Study of Mycobacterium w Plus Docetaxel for Hormone Refractory Metastatic Prostate Cancer (HRPC)"

The protocol admits patients with prostate cancer who have become refractory to hormone therapy and also has developed metastasis. This is a controlled trial wherein efficacy of Mycobacterium w plus Docetaxel is compared with Docetaxel alone (Standard of Care).

The investigations are at several prominent hospitals in India. The investigators have no difficulty, to the best of my information and belief, in using the present invention. The health regulatory authorities who approved the trials had no difficulty, to the best of my information and belief, in understanding how to use the invention.

c) Study NCT00694915 (US FDA) : "Study of Mycobacterium w in Superficial Transitional Cell Carcinoma of Bladder (STCC)"

The protocol admits patients with newly diagnosed superficial transitional cell carcinoma with completely resected papillary tumors and high probability of recurrence risk i.e. stage T1 Grade 2, T1 Grade 3 & CIS. This is a controlled study to compare efficacy of Mycobacterium w intradermal to intravesical BCG (Standard of care) in patients with superficial bladder cancer.

The investigations are at several prominent hospitals in India. The investigators have no difficulty, to the best of my information and belief, in using the present invention. The health regulatory authorities who approved the trials had no difficulty, to the best of my information and belief, in understanding how to use the invention.

d) Study NCT00680940 (US FDA): A Study of Mycobacterium w in Combination with Paclitaxel Plus Cisplatin in Advanced Non Small Cell Lung Cancer (NSCLC)

The protocol admits patients with advanced small cell lung cancer. This is a controlled study to compare efficacy of Mycobacterium w in combination with Paclitaxel plus Cisplatin in advanced non small cell lung cancer to that of Paclitaxel plus Cisplatin (Standard of Care).

The investigations are at several prominent hospitals in India. The investigators have no difficulty, to the best of my information and belief, in using the present invention. The health regulatory authorities who approved the trials had no difficulty, to the best of my information and belief, in understanding how to use the invention.

14. Taking account of my own education and experience and that of colleagues in Cadila and at other research interest companies and in universities and government research and regulatory agencies, it is my opinion, and to the best of my information and belief, would be the opinion of such colleagues, that undue experimentation is not required to practice the making and use of the present invention, i.e., that such practice is enabled by the present specification.

15. I am available to respond to further specific questions the Examiner may have, if any.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under Section 1001 of Title 18 of the United State Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

August 13th 2010 By: Khamar B. M.

Bakulesh Khamar